Remarks

Claims 1 through 15 are presently pending in the application. Claims 1 through 11, 14 and 15 stand withdrawn from consideration as directed to a non-elected invention. Claims 12 and 13 are presently under examination.

Regarding the Claim Objections

Claims 12 and 13 are objected to for allegedly reciting non-elected inventions. While the Office will conduct its search with regard to the elected species, Applicants respectfully maintain that there is no requirement to amend the pending claims so as to remove recitation of non-elected species.

Regarding the Information Disclosure Statement

The Office Action, at page 3, indicates that the Information Disclosure Statement filed January 19, 2001, fails to comply with the provisions of the Manual for Patent Examining Procedure because references 60-1000 lack indication of author and date on the Form 1449. Applicants will prepare and file a revised Form 1449 with the requested information for references 60-100, which refer to Genbank Accession Numbers, as a supplemental response.

Rejections under 35 U.S.C. § 112, First Paragraph

The objection to the specification and corresponding rejection of claims 12 and 13 under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification so as to enable one skilled in the art to practice the claimed invention is respectfully traversed.

The Office alleges, at page 3, first complete paragraph, of the Action mailed September 17, 2003 (Paper No. 16), that the specification does not clearly set forth a mammalian syndrome or disorder that can be diagnosed or treated with the claimed methods nor provide data that correlate mammalian and Drosophila disorders or gene products. In particular, to support the rejection, the Office asserts that "it is not known what the mammalian correlate of the BiP protein is." Also, it is alleged that it is unclear what a "vigilance gene profile" is and how changes in the profile can be correlated with successful treatment of a disorder.

Applicants respectfully disagree with the Examiner's assertions with regard to the alleged lack of enablement for the reasons that follow. Applicants respectfully submit that, given the detailed guidance and teachings provided by the specification, the skilled person would have been able to select a vigilance disorder and establish a corresponding vigilance gene profile via routine methods known in the art and not requiring undue experimentation. Furthermore, armed with these teachings the skilled person would have been able to practice the claimed methods of determining the efficacy of a compound in ameliorating a vigilance disorder and modulating vigilance without undue experimentation.

First, it is respectfully submitted that, contrary to the assertion in the current Office Action, the specification does provide data correlating mammalian and *Drosophila* gene products. In particular, the Examiner asserts in the current Action, at page 3, first complete paragraph, that "it is not known what the mammalian correlate of the BiP protein is." In fact, the

BiP protein was originally identified in mammals. Furthermore, the specification teaches exemplary vigilance-modulated genes identified in *Drosophila melanogaster*, with their sequence identifiers or GenBank Accession Nos. in brackets, and the GenBank Accession Nos. of their apparent rat or human homologs: an apparent homolog of mammalian *Fatty acid synthase* (*Fas*) (contains SEQ ID NO:1; human:NM_004104); *Cytochrome oxidase C, subunit I (mt:Co1)* (J01404, J01405, and J01407; rat:J01435); *Cytochrome p450* (*Cyp4e2*) (X86076; rat:U39206; human:AF054821)); ***BiP*** **(also known as Hsc70-3) (L01498; contains SEQ ID NO:7; human:AF188611)**; and *arylalkyamine N-acetyl transferase* (*Dat*) (Y07964; human:NM_001088) (specification, page 19, lines 1-12).

The specification further teaches and exemplifies that each of these genes was expressed at higher levels during waking than during sleep (see Example IV) (specification, page 19, lines 12-13). In contrast, a gene designated "Rest" was 45% higher during sleep than during rest (specification, page 19, lines 12-14).

As demonstrated in the specification, vigilance-modulated genes in invertebrates include homologs of genes whose expression levels vary with the vigilance state of mammals (specification, page 19, lines 12-14). In this regard the specification provides teachings with regard to the similarity that exists between vigilance-modulated gene expression in rats and in *Drosophila melanogaster*, both in terms of number and type of genes that are modulated (specification, page 19, lines 12-14). Furthermore, Example IV of the specification demonstrates that *Cytochrome oxidase C, subunit I* shows a rapid increase in expression during the first few hours of waking in both rats and *Drosophila*, and further exemplifies that expression of a *Drosophila* and a rat *Cytochrome P450* (U39206, U39207) are similarly upregulated in waking and sleep deprivation (specification, pages 86-94).

Further with regard to mammalian homologs, the specification discloses that a variety of vigilance-modulated genes in rats are described in Cirelli et al., Mol. Brain Res. 56, 293 (1998); Cirelli et al., Ann. Med. 31:117 (1999); Cirelli et al., Sleep 22(S):113 (1999), and sets forth the following genes, along with their GenBank Accession Numbers given in brackets: immediate-early genes, transcription factors and chaperones (e.g. *NGFI-A* (M18416), *NGFI-B* (U17254), *Zn-15* related zinc finger (*rlf*; U22377) , *Arc* (U19866), *JunB* (X54686) and *IER5* (AW142256)); mitochondrial genes (e.g. *Cytochrome oxidase C subunit 1* (J01435), *Cytochrome oxidase C subunit IV* (X54802, M37831, AA982407), *NADH dehydrogenase subunit 2* (NC_001665), *12S rRNA* (J01438) and *F1-ATPase subunit alpha* (X56133); and other genes, including neurogranin (*Ng/RC3*; U22062), bone morphogenetic protein 2 (Z25868), glucose-regulated protein 78 (GRP78; M19645), brain-derived neurotrophic factor (*BDNF*; M61178), interleukin-1β (*IL-1β*; D21835), dendrin (Y09000), and Ca^{++}/calmodulin-dependent protein kinase II (α-subunit) (J02942) (specification, page 20, lines 3-20). Further with regard to mammalian homologs, the specification provides citations of Chemelli et al., Cell 98:437-451, for a description of orexin and its receptor, which regulate sleep and wake in mice; and Cortelli et al, J. Sleep Res. 8(S):23-29, which describes the prior protein gene (PRNP) associated with the vigilance disorder fatal familial insomnia (specification, page 20, lines 20-25).

As further guidance to the skilled person regarding mammalian homologs previously undisclosed as vigilance-modulated genes, the specification describes genes identified by differential display analysis performed according to the methods described in Cirelli et al., Mol. Brain Res. 56, 293 (1998), including *Cytochrome P450* (*Cyp4F5*) (U39206, U39207), AA117313, *aryl sulfotransferase IV* (X68640; S42994), human breast tumor autoantigen homolog (LM04; U24576), an apparent KIAA313 homolog (contains SEQ ID NO:15; similar to human gene AB002311), and membrane protein *E25* (AF038953)(specification, page 20, line 26, to page 21, line 4). The specification also provides additional mammalian nucleotide sequences that are upregulated during wake or sleep and discloses that the invertebrate homologs of each of these genes are considered to be vigilance-modulated genes)(specification, page 21, lines 7-10).

Overall, the specification provides significant teachings that correlate mammalian and *Drosophila* gene products. Similarly, significant teachings are provided to the skilled person with regard to what constitutes a vigilance disorder.

The specification teaches that a vigilance disorder can be any condition that disturbs the normal sleep and wake patterns of an individual (specification, page 62, lines 5-7); can have a genetic or familial basis; can have a psychiatric or medical basis; can be induced by substances including medications and drugs; or can have any combination of these underlying causes (specification, page 62, lines 7-11). Also disclosed are exemplary vigilance disorders including various forms of insomnia, hypersomnia, narcolepsy, parasomnias, sleepwalking disorder, sleep apnea, restless legs syndrome (RLS) and fatal familial insomnia (specification, page 62, lines 11-15). Further with regard to a vigilance disorder, the specification indicates that variety of vigilance disorders in humans are described in Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (1994), published by the American Psychiatric Association (specification, page 62, lines 15-18). Given this guidance, the skilled person would have been able to identify and select a vigilance disorder useful for practicing the methods of the invention.

A vigilance gene profile refers to any read-out that provides a qualitative or quantitative indication of the expression or activity of a single vigilance gene, or of multiple vigilance genes (specification, page 65, lines 17-20). A vigilance gene is a gene that experiences activity changes as a consequence of behavioral state. A vigilance gene profile can, for example, indicate the expression or activity of one, or of least 2, 5, 10, 20, 50, 100 or more vigilance and also can, for example, indicate the expression or activity in mammals of mammalian homologs of one or more vigilance genes identified as such from the invertebrate screening assays described in the specification, such as *Fas, BiP, Cyp4e2, AANAT1 (Dat), Ddc*, or a gene containing any of SEQ ID NOS:2-6 (specification, page 65, lines 20-28). Claims 12 and 13 recite and the specification teaches that at least one of the vigilance genes profiled is selected from the group consisting of *Fas, BiP, Cyp4e2, AANAT1 (Dat), Ddc, Cytochrome P450,*

AA117313, *aryl sulfotransferase IV*, human breast tumor autoantigen homolog, KIAA313 homolog, *E25*, and a gene containing SEQ ID NOS:2-6, 8-14, or 16-27 or modification thereof (specification, page 65, line 28 to page 66, line 4).

As further guidance to the skilled person the specification discloses that a vigilance gene profile can indicate the expression or activity of one or more vigilance genes identified as such from published mammalian studies described above, including *NGFI-A*, *NGFI-B* , rlf, *Arc, JunB, IER5, Cytochrome oxidase C subunit 1, Cytochrome oxidase C subunit IV, NADH dehydrogenase subunit 2, 12S rRNA F1-ATPase subunit alpha*, Ng/RC3, bone morphogenetic protein 2, GRP78, BDNF, IL-1β, dendrin, Ca^{++}/calmodulin-dependent protein kinase II α-subunit, orexin, orexin receptor, and PRNP (specification, page 66, lines 4-13). A vigilance gene profile can be, for example, a quantitative or qualitative measure of expression of mRNA expressed by a vigilance gene (specification, page 66, lines 21-23). The specification discloses a variety of routine methods of detecting or quantitating mRNA expression that have been described in connection with invertebrate screening assays and include, without limitation, Northern or dot blot analysis, primer extension, RNase protection assays, differential display, reverse-transcription PCR, competitive PCR, real-time quantitative PCR (TaqMan PCR), and nucleic acid array analysis (specification, page 66, lines 23-30).

Additional enablement regarding a vigilance gene profile is provided by the teaching that the profile can be, for example, a quantitative or qualitative measure of expression of polypeptides encoded by vigilance genes (specification, page 67, lines 1-4). In this regard, the specification discloses a variety of routine methods of detecting or quantitating protein expression have been described in connection with invertebrate screening assays, and include, but are not limited to, immunohistochemistry, immunofluorescence, immunoprecipitation, immunoblot analysis, and various types of ELISA analysis, including ELISA analysis using arrays of vigilance-polypeptide specific antibodies bound to solid supports, as well as additional

methods including two-dimensional gel electrophoresis, MALDI-TOF mass spectrometry, and ProteinChip^{TM}/SELDI mass spectrometry technology (specification, page 67, lines 4-13).

The specification further teaches that a vigilance gene profile a direct or indirect measure of the biological activity of polypeptides encoded by vigilance genes (specification, page 67, lines 14-16). As further guidance, the specificaton teaches direct measures of the biological activity of a vigilance polypeptide, including, measures of enzymatic activity,as well as indirect measures such as the polypeptide's state of modification (e.g. phosphorylation or glycosylation), localization (e.g. nuclear or cytoplasmic), abundance of a substrate or metabolite of the polypeptide, such as a neurotransmitter (specification, page 67, lines 16-29). The specification also teaches that a vigilance gene profile can be established *in vivo*, such as by diagnostic imaging procedures using detectably labeled antibodies or other binding molecules, or from a sample obtained from an individual that can contain, for example, neural tissue, cells derived from neural tissues, or extracellular medium surrounding neural tissues, in which vigilance polypeptides or their metabolites are present such as human cerebrospinal fluid (specification, page 68, lines 14-27).

Further with regard to enablement of a vigilance gene profile, the specification teaches that the vigilance gene(s) to be profiled can be determined by those skilled in the art, depending on the type of vigilance-altering compound it is desired to identify or characterize (specification, page 72, lines 8-11). It is further taught that an expression or activity profile of one or many vigilance genes can be established that is a molecular fingerprint of each mammalian vigilance level, state or disorder of interest and, further, that, in screening applications, identification of vigilance genes and their role in vigilance allows novel vigilance-altering compounds to be identified, lead compounds to be validated, and the molecular effects of these compounds and other known vigilance-altering compounds to be characterized, by determining the effect of these compounds on a vigilance gene profile (specification, page 44, lines 18-27).

The specification further teaches that it may be advantageous to examine the effect of a compound primarily on single genes whose causative role in vigilance has been established, including *Dat*, *Ddc*, orexin, orexin receptor and PRNP; or only or primarily on those vigilance genes whose expression or activity is upregulated during sleep; or only or primarily on those vigilance genes whose expression or activity is upregulated during wake; or only or primarily on those genes whose expression is modulated during sleep rebound, during sleep-wake transition, or in the period following restorative or disrupted sleep (specification, page 72, lines 8-21). The specification also teaches that a additional vigilance genes can be identified by a variety of methods in addition to the exemplified methods, including differential display, arrays, and other forms of expression or activity analysis in invertebrates and mammals; genetic methods, such as by randomly or specifically targeting genes in model organisms such as *Drosophila* or mouse, or by mapping genes associated with vigilance disorders or altered vigilance properties; or from screens for genes associated with other behaviors or molecular pathways that are subsequently determined to be associated with vigilance (specification, page 73, lines 16-26).

Given the teachings provided by the specification, the skilled person would have been able to select a vigilance disorder and establish a corresponding vigilance gene profile via routine methods known in the art and not requiring undue experimentation. Furthermore, armed with these teachings the skilled person would have been able to practice the claimed methods of determining the efficacy of a compound in ameliorating a vigilance disorder and modulating vigilance without undue experimentation. Accordingly, Applicants respectfully request removal of the rejection of claims 12 and 13 under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification so as to enable one skilled in the art to practice the claimed invention.

Rejections under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 12 and 13 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention, respectfully is traversed. Applicants submit that the terms cited by the Examiner as indefinite is clear and definite in view of the specification for the reasons which follow.

Given that definiteness of claim language must be analyzed, not in a vacuum, but in light of the content of the particular application disclosure, the teachings of the prior art, and the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time of the invention, Applicants submit that the person of ordinary skill would have considered claims 12 and 13, including the terms "vigilance disorder" and "vigilance gene," as clear and definite at the time of filing.

The specification, at page 43, lines 21-26, clearly defines "vigilance genes" as genes that are either vigilance-modulated or vigilance-altering.

First, the term "vigilance-modulated gene" is further clearly defined as referring to a gene whose expression level varies according to vigilance state (specification, page 18, lines 10-25). Here, the specification further describes that, for example, the expression level of a vigilance-modulated gene can normally vary by at least about 10%, such as at least 25%, or at least about 50%, including at least about 100%, 250%, 500%, 1000% more between sleep and wake. The specification also describes that at least about 1% of the transcripts in invertebrates are modulated by vigilance state and, consequently, correspond to vigilance-modulated genes. The specification further describes that in the methods of the invention one can evaluate expression of at least one vigilance-modulated gene, such as at least 2, 5, 10, 20, 50, 100 or more vigilance-modulated genes.

Second, the term "vigilance-altering gene" is also clearly defined as referring to a gene whose expression level can, but does not need to, vary with vigilance state, but whose function influences or is required for inducing or maintaining a vigilance level or a vigilance property (page 21, line 27, to page 22, line 6). Exemplary functions of a vigilance-altering gene that can be evaluated include transcriptional or translational regulatory activity, and phosphorylation, dephosphorylation, glycosylation or other post-translational modification.

In addition to clearly defining the above terms, the specification provides numerous examples of vigilance genes, including both vigilance-modulated and vigilance-altering genes as well as mammalian homologs (specification, for example, pages 20-24).

The specification defines a vigilance disorder as any condition that disturbs the normal sleep and wake patterns of an individual (specification, page 62, lines 5-7). The specification further discloses that a vigilance disorder can have a genetic or familial basis; can have a psychiatric or medical basis; can be induced by substances including medications and drugs; or can have any combination of these underlying causes (specification, page 62, lines 7-11). Also disclosed are exemplary vigilance disorders including various forms of insomnia, hypersomnia, narcolepsy, parasomnias, sleepwalking disorder, sleep apnea, restless legs syndrome (RLS) and fatal familial insomnia (specification, page 62, lines 11-15). Further with regard to a vigilance disorder, the specification indicates that variety of vigilance disorders in humans are described in Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (1994), published by the American Psychiatric Association (specification, page 62, lines 15-18).

Finally, the Examiner asserts that, with regard to a vigilance disorder, that some of the disorders are not genetically based and, therefore, would not be amenable to treatment via the invention methods. Applicants respectfully disagree and submit that the existence of a genetic basis of a vigilance disorder is not a prerequisite for treatment via the invention methods. Rather, the ability of a compound to modulate the vigilance gene profile of an individual to

correspond to a normal vigilance profile indicates that the compound is effective in ameliorating a vigilance disorder, regardless of whether the disorder has a genetic basis.

In view of the above arguments, Applicants respectfully request removal of the rejection of claims 12 and 13 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

Conclusion

In light of the Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to contact the undersigned attorney with any questions related to this application.

Respectfully submitted,

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